

AMENDMENTS TO THE SPECIFICATION

In the originally-filed specification, please delete the paragraph spanning page 31, line 27 – page 32, line 9 and replace with the following amended paragraph:

The rabbit model of hindlimb ischemia (Takeshita, S., et al. *J.Clin.Invest.* (1994)) was employed to determine if cytokine-induced EPC mobilization could enhance neovascularization of ischemic tissues. To effect GM-CSF-induced EPC mobilization while avoiding a direct effect on ECs, recombinant human GM-CSF was administered daily for 7 days *prior to* ~~to~~ development of hindlimb ischemia. Such GM-CSF pre-treatment (50µg/day s.c.) increased the EPC-enriched population (12.5 ± 0.8 vs $6.7 \pm 0.3 \times 10^5$ /ml, $p < 0.01$) and enhanced EPC differentiation (423 ± 90 vs 100 ± 19 /mm², $p < 0.01$) at day 0 (day 7 of pre-treatment prior to surgery). By post-operative day 7, the frequency of circulating EPCs and EPC differentiation in GM-CSF-pretreated group exceeded control values (20.9 ± 1.0 vs $11.3 \pm 2.5 \times 10^5$ /ml [$p < 0.05$], 813 ± 54 vs 539 ± 73 /mm² [$p < 0.01$]) respectively (Figures 6A, 6B). Capillary density analysis documented extensive neovascularization induced by GM-CSF pre-treatment (249 ± 18 vs 146 ± 18 /mm² in untreated controls, $p < 0.01$), as well as improved ischemic/normal hindlimb blood pressure ratio (0.71 ± 0.03 vs 0.49 ± 0.03 , $P < 0.01$) (Figure 6C).

In the originally-filed specification, please delete the paragraph spanning page 34, line 24 – page 35, line 9 and replace with the following amended paragraph:

The discussion and Examples above addressed the significance of ~~We investigated~~ the endogenous stimuli, namely tissue ischemia, and exogenous cytokine therapy, specifically granulocyte macrophage-colony stimulating factor (GM-CSF), in the mobilization of EPCs and induction of neovascularization of ischemic tissues. Development of regional ischemia in both mice and rabbits was found to increase the frequency of circulating EPCs. In mice, the impact of ischemia-induced EPC mobilization was shown by enhanced ocular neovascularization following cornea micropocket surgery in animals with hindlimb ischemia compared to non-ischemic controls. In rabbits with hindlimb ischemia, circulating EPCs were further augmented following GM-CSF pre-treatment, with a corresponding improvement in hindlimb neovascularization. Direct evidence that EPCs which contributed to enhanced corneal

neovascularization were specifically mobilized from the bone marrow (BM) in response to ischemia and GM-CSF was documented in mice transplanted with BM from transgenic donors expressing ~~β -galactosidase~~ β -galactosidase transcriptionally regulated by the endothelial cell (EC) specific Tie-2 promoter. These findings indicate that circulating EPCs are mobilized endogenously in response to tissue ischemia or exogenously by cytokine therapy and thereby augment neovascularization of ischemic tissues.